IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NOVOZYMES A/S, Plaintiff v. GENENCOR INTERNATIONAL, INC., and ENZYME DEVELOPMENT CORPORATION Defendants	C.A. No. 05-160-KAJ

PLAINTIFF NOVOZYMES' POST-TRIAL OPPOSITION BRIEF

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TABLE OF CONTENTS

Page

I. INTRODUCTION 1

II. STATEMENT OF THE CASE 2

III. ARGUMENT 8

A. The '031 Patent Is Enforceable 8

1. There Was No Inequitable Conduct Surrounding Machius '95 10

2. The Borchert Declaration 15

B. THE '031 CLAIMS ARE VALID 20

1. Claims 1, 3 and 5 Are Non-Obvious 20

(a) The Combination of Suzuki and Bisgärd-Frantzen Does Not Make the '031 Claims Obvious 21

(b) The Borchert Declaration Demonstrates Unexpected Results 22

(c) Machius '95 Does Not Render the Claims Obvious 24

(d) Objective Considerations of Nonobviousness 26

2. The Claims Are Enabled By the Specification 26

C. Claim Construction 27

1. Parent Bacillus Stearothermophilus Alpha-Amylase 28

(a) SEQ. ID NO. 3 Is Not the Only Parent or the Only B. stearothermophilus Alpha-Amylase 28

(b) The Parent and B. Stearothermophilus Alpha-Amylase Do Not Require 514 or 515 Amino Acids Minus the Signal Sequence 31

(c) G997 Is A "B. stearothermophilus Alpha-Amylase" 33

2. Percent Homology Means Percent Identity According to GAP; Not Counting Unmatched Residues 36

TABLE OF CONTENTS
(Continued)

Page

D. Genencor and Spezyme Ethyl Infringe Claims 1, 3 and 5 39

IV. CONCLUSION 40

TABLE OF AUTHORITIES

Page

Federal Cases

3M Innovative Prop. Co. v. Avery Dennison Corp.,
350 F.3d 1365 (Fed. Cir. 2003).....31

Amgen Inc. v. Hoechst Marion Roussel,
314 F.3d 1313 (Fed. Cir. 2003).....10

Application of Snoddy,
420 F.2d 381 (C.C.P.A 1970).....16

Chiron Corp. v. Genentech, Inc.,
363 F.3d 1247 (Fed. Cir. 2004).....27

Dayco Prods., Inc. v. Total Containment, Inc.,
329 F.3d 1358 (Fed. Cir. 2003).....12

Digital Control, Inc., v. Charles Mach. Works,
437 F.3d 1309 (Fed. Cir. 2006).....8

Demaco Corp. v. F. Von Langsdorff Licensing Ltd.,
851 F.2d 1387 (Fed. Cir. 1988).....26

eSpeed, Inc. v. Brokertec USA, L.L.C.,
417 F. Supp. 2d 580 (D. Del. 2006).....10

FMC Corp. v. Hennessy Industries, Inc.,
836 F.2d 521 (Fed. Cir. 1987).....8

FMC Corp. v. Manitowoc Co.,
835 F.2d 1411 (Fed. Cir. 1987).....8, 11

Fromson v. Advanced Offset Plate,
755 F.2d 1549 (Fed. Cir. 1985).....26

Graham v. John Deere Co.,
383 U.S. 1 (1966).....24, 26

Hebert v. Lisle Corp.,
99 F.3d 1109 (Fed. Cir. 2000).....8, 13

In re Chupp,
816 F.2d 643 (Fed. Cir. 1987).....15, 16

In re Dillon,
892 F.2d 1554 (Fed. Cir. 1989).....16

TABLE OF AUTHORITIES
(Continued)

Page

In re Dow Chemical,
837 F.2d 469 (Fed. Cir. 1988) 20, 22

In re Finley,
174 F.2d 130 (CCPA 1949) 16

In re Merchant,
575 F.2d 865 (CCPA 1978) 16

In re Rouffet,
149 F.3d 135 (Fed. Cir. 1998) 26

In re Soni,
54 F.3d 746 (Fed. Cir. 1995) 18, 22, 24

In re Vaeck,
947 F.2d 488 (Fed. Cir. 1991) 20, 22

Johns Hopkins Univ. v. Cellpro, Inc.,
152 F.3d 1343 (Fed. Cir. 1998) 27, 38

Kao Corp. v. Unilever U.S., Inc.,
441 F.3d 963 (Fed. Cir. 2006) 10, 14, 22

Kingsdown Med. Consultants, Ltd. v. Hollister, Inc.,
863 F.2d 867 (Fed. Cir. 1988) 9, 14, 15

Knowles v. Tibbets,
347 F.2d 591 (C.C.P.A. 1965) 16

Kraft Foods, Inc. v. Int'l Trading Co.,
203 F.3d 1362 (Fed. Cir. 2000) 29

Marley Mouldings, Ltd. v. Mikron Indus.,
417 F.3d 1356 (Fed. Cir. 2005) 38

N. Telecom Ltd. v. Samsung Elecs. Co.,
215 F.3d 1281 (Fed. Cir. 2000) 32

nCube Corp. v. SeaChange Int'l, Inc.,
436 F.3d 1317 (Fed. Cir. 2006) 29

Northern Telecom, Inc. v. Datapoint Corp.,
908 F.2d 931 (Fed. Cir. 2003) 8

Paivinen v. Sands,
339 F.2d 217 (C.C.P.A. 1964) 16

TABLE OF AUTHORITIES
(Continued)

Page

PerSeptive Biosystems, Inc. v. Pharmacia Biotech, Inc.,
225 F.3d 1315 (Fed. Cir. 2000).....10

Phillips v. AWH Corp.,
415 F.3d 1303 (Fed. Cir. 2005).....27, 28, 32, 37

Pro-Mold and Tool Co. v. Great Lakes Plastics, Inc.,
75 F.3d 1568 (Fed. Cir. 1996).....10

Purdue Pharma L.P. v. Endo Pharms, Inc..,
438 F.3d 1123 (Fed. Cir. 2006).....8, 28

Regents of the Univ. of Cal. v. Eli Lilly & Co.,
119 F.3d 1559 (Fed. Cir. 1997).....10

Renishaw PLC v. Marposs Societa' per Azioni,
158 F.3d 1243 (Fed. Cir. 1998).....28

Richards-Vicks, Inc. v. Upjohn Co,
122 F.3d 1476 (Fed. Cir. 1997).....25

Scripps Clinic & Research Foundation v. Genentech, Inc.,
927 F.2d 1565 (Fed. Cir. 1991).....11, 14

Sri Int'l v. Matsushita Elec. Corp.,
775 F.2d 1107 (Fed. Cir. 1985).....32

Sunrace Roots Enter. v. SRAM Corp.,
336 F.3d 1298 (Fed. Cir. 2003).....27, 28, 29

Tandon Corp. v. U.S. Int'l Trade Comm'n,
831 F.2d 1017 (Fed. Cir. 1987).....27, 29

Tap Pharm. Prods., Inc. v. Owl Pharms., L.L.C.,
419 F.3d 1346 (Fed. Cir. 2005).....10

Unitherm Food Systems, Inc. v. Swift Eckrich, Inc.,
375 F.3d 1341 (Fed. Cir. 2004).....27, 28, 37

Uttler v. Hiraga,
845 F.2d 993 (Fed. Cir. 1988).....27

Vitronics Corp. v. Conceptronic Inc.,
90 F.3d 1576 (Fed. Cir. 1996).....27, 28, 37, 38

Voisinet v. Coglianese,
455 F.2d 1064 (C.C.P.A. 1972).....16

TABLE OF AUTHORITIES
(Continued)

Page

Federal Statutes & Administrative Codes

35 U.S.C. § 112 27

35 U.S.C. § 282 22

37 C.F.R. § 1.56 10

I. INTRODUCTION

The essence of Genencor's defense to its bold infringement of Novozymes' '031 patent is that competition must have spurred Novozymes to formulate a "plan," by which it intentionally withheld the Machius '95 reference and overstated unexpected results in the Borchert Declaration. According to Genencor, this makes the patent obvious, invalid, and unenforceable; excusing its deliberate infringement. **GPTB, at 1-2.**[1] In fact, it was Genencor that knew of Novozymes' intention to patent the 179,180 *B. stearothermophilus* ("BSG") alpha-amylase variants long before Novozymes learned of Genencor's "plan" to sell the infringing Spezyme Ethyl product anyway. **NPF, ¶412**. It is Genencor that provoked Novozymes, and took the risk of infringement. It is Genencor that hopes to escape with a classic blame-the-victim "plan."

At trial it was shown that Machius '95 is less relevant prior art than Suzuki and Bisgärd-Frantzen, cited by the PTO. **NPF, at ¶¶216-232, 253-55, 358-66, 393-401**. Machius added nothing to further motivate a protein engineer. Its contradictory and confusing theories made the claimed invention no more predictable. **NPF, ¶¶216-232**. Machius could not explain why Suzuki's *B. amyloliquefaciens* ("BAN") experiment had worked, which is not relevant anyway. ***Id.*** Further, the Borchert Declaration was fair, and the claimed variants provide an important and unexpected improvement. **NPF, ¶¶ 181-215, 349-57**. There is no clear and convincing proof of obviousness; the claimed invention is sound and patentable. **NPF, ¶¶339-375**. There was no inequitable conduct either; the patent was legitimately secured. Nothing material was withheld or misrepresented. The only evidence is that Novozymes and its counsel acted in good faith. **NPF, ¶¶383-408**.

Genencor cannot wriggle off the hook by concocting *ad hoc* non-infringement excuses, based on extrinsic claim limitations found nowhere in the claims themselves, in the patent, or from the file history. The terms "parent" and "*B. stearothermophilus* alpha-amylase" have their customary meanings, which cannot be altered to mean other and different things, like "SEQ. ID

[1] Genencor's Proposed Findings are cited as **GPF, ¶X**; its Proposed Conclusions of Law are **GCL, ¶X**; and its Post Trial Brief is "**GPTB at X.**" Novozymes' Proposed Findings & Conclusions are cited as **NPF, ¶X**; and its Post-Trial Brief is "**NPTB at X.**"

NO. 3" or "514-515 amino acids minus the signal sequence." **NPF, ¶¶78-89**. The patent expressly provides a customary meaning of "percent homology" as "percent identity," calculated in a standard way according to a common implementation (GAP). This definition cannot be replaced by other methods, extraneous to the patent. **NPF, ¶¶90-101**. Genencor admits infringement when the claims are interpreted according to their ordinary usage, as Novozymes has done. **GPTB, at 16-20**. This is the correct claim construction, and Genencor's infringement is plain.

Genencor cannot side-step the patent by rewriting it; nor by polluting the facts with noxious inferences, drawn from the fact of competition between the parties. Genencor cannot escape by saying that commercial interest motivates a patent strategy (or in its own case, an anti-patent strategy). Genencor forcefully went ahead with the infringing 179,180 BSG variant in Spezyme Ethyl. This cannot make a miscreant of Novozymes, and makes Genencor a willful infringer.

II. STATEMENT OF THE CASE

Novozymes is the largest producer of industrial enzymes in the world. **NPF, ¶3**. Through a combination of insight, trial and error, hard work, and luck, enzymes are modified at the amino acid level, by protein engineering, to improve their properties for industry. **NPF, ¶8-28**. Genencor is Novozymes' principal competitor in this business. **A5586:8-5587:15.**

Novozymes invented a number of alpha-amylase variants by the mid-1990s, and filed Danish patent applications for some of this work in February 1995. **NPF, ¶37; TE-100, A7002**. International (PCT) and U.S. applications were filed in February 1996. ***Id.*** This led to three U.S. patents, including the '031 patent, each with the same disclosure. ***Id.***; **NPF, ¶266-67; A7002**. Novozymes commercialized one of the variants it invented as Liquozyme SC, a highly successful alpha-amylase for liquefying starch in the fuel ethanol industry. **GPTB, at 2**; **A8855**; **A6028:11-25; A6029:19-23**. Novozymes sought patent claims for its commercial product **(TE-501, A8560-8601; A8697-8700)**, and then followed up on other disclosed embodiments, including the 179,180 BSG variants now in suit. **TE-100, A7002, A7040; TE-101, A7045-48**.

Claims for the 179,180 BSG variants were presented to the PTO by December 19, 2001, before Novozymes knew of Genencor's "plan" to adopt these variants for Spezyme Ethyl. **TE-101 at A7045-46; NPF, ¶45-51, 412; A1006.**[2] In the usual way, the claims were rejected (**NPF, ¶52-59**), and Novozymes worked to overcome the rejection in a classic back-and-forth with the PTO. **NPF, ¶60-66**. The Examiner thought it would be obvious to alter a BSG alpha-amylase the way Suzuki altered *B. amyloliquefaciens* ("BAN") alpha-amylase, to get a similar thermostability increase, because Bisgärd-Frantzen said that BAN and BSG are highly homologous. **NPF, ¶59; GPTB at 24, n.9**. Novozymes narrowed the 179,180 BSG claims to add an amino acid alteration involving cysteine, and the rejections were argued. **NPF, ¶60**.

The broader 179,180 BSG claims were important and Novozymes did not abandon them. **TE-110, at A8169-71**. Even before it knew of Genencor's plan to use Spezyme Ethyl against LiquozymeSC, Novozymes went forward with an experiment to compare a claimed 179,180 BSG variant to the closest prior art: the BAN variant of Suzuki, cited by the Examiner. This work was fairly planned and carried out. **NPF, ¶181-215, 349-52, 402-08**. The test conditions were appropriate for all the enzymes being compared, and correctly modeled their industrial use at high temperature and low calcium. **NPF, ¶193-99**. The data was collected, analyzed and reported using good scientific method and accepted standards of care. **NPF, ¶200-215; TE-508, at A8857-74**. Novozymes appreciated that the work might show an unexpected improvement, or it might not. **A5641:7-19**. Either way, good or bad results would have to be disclosed to the PTO. **NPF, ¶259**.

The results were not foreseeable or ho-hum. The 179,180 BSG variant demonstrated an unexpectedly superior increase in thermostability under stress compared to BAN, at high temperature and low calcium. **NPF, ¶184, 191-92**. This supported patentability and led to allowance of the '031 claims in suit. **NPF, ¶64-66**. No other experiment has been presented to say otherwise. These facts are also consistent with Genencor's selection of a 179,180 BSG variant as its needed high performance alpha-amylase. **A5031:19-A5039:11; NPF, ¶118-27; GCL, ¶19**.

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[2] *See also* **A7039:12-7041:1, A7049:9-24; A5032:2-8; A5034:24-5035:2; A5040:1-14**.

Genencor had no product to compete with Liquozyme SC, and sought long, hard, and unsuccessfully to get one. **A5031:19-A5039:11**. Genencor turned to a 179,180 BSG variant as the only alternative it could find. ***Id***. Genencor was so bent on finding a "me too" product that it bought an entire company, EBS, at least in part for the "EBS2" alpha-amylase that is now marketed as Spezyme Ethyl. ***Id***.; **A5048:23-5049:24; A5038:6-5039:11**. Genencor went ahead, knowing that EBS2 is a 179,180 BSG deletion variant. Genencor took a calculated risk and went ahead with Spezyme Ethyl, despite its knowledge that the '031 claims for 179,180 BSG variants were "patent pending," and would likely be infringed. **NPF, ¶412**. Genencor did not alter course when it was told these claims were allowed by the PTO. ***Id*; A5031:19-A5039:11**.

There is no real dispute that Spezyme Ethyl is a 179,180 BSG variant as described and claimed in the patent. Genencor concedes that "Spezyme Ethyl has alpha-amylase activity" (**GCL, ¶20**), and further (**GCL, ¶19**):

> Spezyme Ethyl is a "variant of a parent *Bacillus stearothermophilus* alpha-amylase," comprising a deletion of amino acids 179 and 180, using SEQ. ID NO. 3 for numbering, because it is missing the two amino acids, arginine and glycine, at positions corresponding to positions 179 and 180 of SEQ. ID NO. 3.

Spezyme Ethyl was derived from a specific wild-type BSG alpha-amylase called G997, and was deliberately constructed so that the only engineered difference between Spezyme Ethyl and its unaltered G997 source or "parent" is the deletion of the amino acids R179 and G180. **GCL, ¶19; NPF, ¶153-57; A5040:1-5041:7; A5045:16-19**. *See* '031 patent (claim 5); **TE-100, A7040**. When Spezyme Ethyl is compared to its parent (G997) for percent homology, calculated according to the patent, it is 100% identical, which is "at least 95%." *See*, '031 patent (claim 1). **NPF, ¶158**. When Spezyme Ethyl is compared to SEQ. ID NO. 3 for percent homology, it is 98.967% identical, which is "at least 95%." *See*, '031 patent (claim 3). **NPF, ¶162-63**.

Genencor reacts by suggesting "many grounds" to excuse its infringement, hoping one will stick. **GPTB at 2**.

For one, Genencor offers novel meanings for "parent" and *B. stearothermophilus* alpha-amylase." These are *different* from what is customary, *different* from what the patent says, *different* from the '031 file history, and *different* from what a protein engineer would know is going on here. *Compare* **GPTB, at 5-11**; **GPF, ¶135-167; GCL, ¶13-15** with **NPF, ¶178-85**. Genencor admits that its Spezyme Ethyl variant was made by deleting residues 179,180 from the wild-type G997 alpha-amylase -- exactly according to the '031 claims. **GPF, ¶57-59; GCL, ¶19**. Genencor admits that G997 is a "parent," and is a wild-type "*B. stearothermophilus* alpha amylase" as those terms are normally used. **GPF, ¶57-59; GCL, ¶19; TE-194, at A8525**. Genencor nonetheless rejects G997 as falling within claims 1 and 5, because G997 variously is not SEQ. ID NO. 3 (**GPTB, at 5-8**), does not have 514 or 515 amino acids (***Id.*, at 8-10**), or is a "disqualified" industrial product (***Id.* at 10-11**). These are slender reeds and straws; grasping them won't help.

SEQ. ID NO. 3 is a reference sequence "for numbering;" it is not the sole "parent" or "*B. stearothermophilus* alpha-amylase" of the '031 disclosure and claims. **NPF, ¶80-84**. SEQ. ID NO. 3 is an exemplary BSG alpha-amylase sequence, but the claims are not so limited. ***Id.*** There is also no requirement for "514 or 515 amino acids," nor for an "encoded" BSG alpha-amylase sequence minus the signal sequence. **NPF, ¶86-89, 138-40**. The claims likewise do not exclude G997 because it was commercialized or industrially produced, nor does G997 have a variable sequence that precludes comparison. The sole sequence for Spezyme Ethyl is admitted. **NPF, ¶128**. There is one G997 sequence that is common to all of the experiments. **NPF, ¶129-37**. It is the one where the only difference from Spezyme Ethyl is the intended difference: deletion of R179 and G180. **NPF, ¶136, 141-42, 154-58; GCL, ¶19**. There is no showing that any other sequence is preponderant or would avoid infringement. **NPF, ¶149**. There is no showing that industrial processing matters for G997 but not for Spezyme Ethyl; there is no reason to treat these enzymes differently. Apples are compared with apples; Genencor's studied ignorance notwithstanding.

For another excuse, Genencor argues that "percent homology" should be calculated in a way that is *different* from what the patent says to do, using *different* programs and methods that the

patent does not mention, and which a protein engineer would not adopt instead. **GPTB, at 11-16**; **NPF, ¶¶90-101**. Genencor agrees that a customary and widely used meaning of "percent homology" is percent identity, as in the patent, calculated according to a standard method also in the patent. **GPTB, at 11**. Genencor concedes infringement if percent homology is calculated in this conventional way. ***Id.*** **at 14-15**. Nevertheless, Genencor would take a different road, less traveled, and without direction from the intrinsic record, hoping the Court will follow. ***Id.*** **at 15-16**. Such detours cannot avoid the plain meaning of the claims and the plain fact of Genencor's infringement.

For yet another excuse, Genencor argues that the Court should resurrect Suzuki and Bisgärd-Frantzen, or breathe life into Machius, because the unexpected results submitted to the PTO in the Borchert Declaration were allegedly overstated. **GPTB, at 20-26**. However, no such proof was made at trial; and certainly not by clear and convincing evidence. **NPTB, at 27-33**. Genencor's microscopic examination of the Declaration showed in the end that the experiment was reasonably done. It was a fair comparison to the closest prior art: Suzuki's BAN mutant. **NPF, ¶181-215**. The improved thermostability of the claimed BSG variant was unpredictable and unexpectedly good compared to BAN, particularly under conditions that are relevant to the invention and the patent. **NPF, ¶184, 191-92**.

The evidence at trial confirmed these findings: the experiment was a reliable representation of what was "really going on with these enzymes," **A6549:23-6550:15**. This improvement provides a coveted industrial product in the face of failed alternatives, especially for high-temperature/low-calcium starch liquefaction. **NPF, ¶191-92**. There is no compelling reason to invalidate the patent for obviousness because of anything in the Borchert experiment or Declaration.

Furthermore, no one manipulated the experiment, the data, the results, or the Declaration. There is no evidence, and no clear and convincing showing, that anyone had any plan or purpose to mislead the PTO. The evidence shows an honest and conscientious scientific effort. **NPF, ¶185, 249-266, 393-408**. Genencor had no contrary data or results, nor would its criticisms change the

outcome. Nothing material was withheld or misrepresented. There was no deceptive intent. There is no compelling reason to strike down the patent for "inequitable conduct."

As a main excuse for its infringement, Genencor makes much of the Machius reference, because it was not considered by the PTO in connection with the '031 claims in suit. **GPTB, at 23-26, 29-33**. Genencor urges that Machius should replace Suzuki and Bisgärd-Frantzen, and was concealed by Novozymes in a conspiracy to get the patent. ***Id.*** In fact, Machius was less relevant, cumulative at best, and added nothing tangible to the closest prior art. There was no duty to cite it. Novozymes certainly believed it was not material, there is substantial evidence of good faith, and no showing that it was withheld intentionally and with turpitude. **NPF, ¶249-56, 393-401**.

As for obviousness, Machius did not lead any closer to the '031 invention, nor predict any greater success than the other prior art. **NPF, ¶216-232, 358-66**. Machius shows that in 1995, alpha-amylase thermostability was not well understood, many uncertain theories were floated, none were satisfactory, and altering these enzymes to achieve a leap in performance was unpredictable. ***Id***. The record shows affirmatively that before the '031 patent, a protein engineer could not predict whether a 179,180 BSG variant would turn out to have improved thermostability, and if so how much. ***Id***. Those in the field could not say that the doubtful Machius crystal structure, for a different *B. licheniformis* ("BLA") alpha-amylase, was a crystal ball for BSG. ***Id***.

Genencor's final complaint is that the patent has claims that intentionally cover Spezyme Ethyl (even while it denies infringement). **GPTB, at 39, n.16; GCL, ¶112-14**. There is nothing wrong with pursuing patent rights and intending to enforce them, even by barring a competitor from the market. This is the purpose of a patent. It is meant to secure for inventors, for a limited time, the exclusive right to make, use and sell their inventions. **U.S. Const., Article I, § 8, cl. 8**. Novozymes had support for its claims and was pursuing them, before it knew about Genencor's plans. **TE-110, at A8169-71**. The prosecution was standard throughout, both before and after Genencor's plans became known. **NPF, ¶38-66, 266-70**. The commercial importance of the patent cannot impugn the Borchert Declaration, nor elevate Machius: they stand on their own. The

Declaration stands up well (**NPF, ¶249-265, 393-408**), while Machius does not. **NPF, ¶216-232**. It was proper for Novozymes to take the time needed to address the prior art, including experimental work. **NPF, ¶266-70, 409-12**. There is no timing problem, no prosecution laches, no detrimental reliance, no invalidity, no inequitable conduct, and no reason to strike down the patent.

III. ARGUMENT

A. The '031 Patent Is Enforceable

Genencor principally attempts to circumvent the '031 patent by alleging that it was procured by inequitable conduct. To do so, it makes a hostile personal attack on scientist and '031 co-inventor Dr. Torben Borchert, and on patent attorney Jason Garbell: accusing them of conspiring to withhold prior art and misrepresent experiments. **GPTB, at 29-39**. However, the trial showed that they acted properly throughout the '031 prosecution. **NPTB, at 36-40.** Genencor did not prove its theory, especially by the high standard of clear and convincing evidence. *Purdue Pharma L.P. v. Endo Pharms, Inc..*, 438 F.3d 1123, 1128-29 (Fed. Cir. 2006); *Digital Control, Inc., v. Charles Mach. Works*, 437 F.3d 1309, 1313 (Fed. Cir. 2006). Instead, Genencor spins a yarn of it own, from innuendo, and with citations to the record that do not support its claims. *Hebert v. Lisle Corp.*, 99 F.3d 1109, 1116 (Fed. Cir. 2000); *FMC Corp. v. Hennessy Industries, Inc.*, 836 F.2d 521 (Fed. Cir. 1987) (no misconduct from a "web of conjecture, inference, and innuendo").

An alleged omission or misrepresentation to the PTO is inequitable only if there is clear and convincing proof that it was material, and there was a manifest intent to mislead. *Purdue,* 438 F.3d at 1128-29; *FMC Corp. v. Manitowoc Co.,* 835 F.2d 1411, 1415 (Fed. Cir. 1987). Omitting prior art that is no more relevant than what the PTO considered is not inequitable. *Id.* Intent cannot too easily be inferred, particularly when there is a reasonable explanation for what happened. *Northern Telecom, Inc. v. Datapoint Corp.,* 908 F.2d 931, 939 (Fed. Cir. 2003).

Contrary to these principles, Genencor tries to set the stage by making much of the fact that Novozymes had an option "plan," for addressing the possible rejection of claims in the PTO, implying illicit conduct by Novozymes from the fact of Genencor's decision to market Spezyme

Ethyl. **GPTB, at 34, 36**. Of course Novozymes had a plan. The plan was to obtain the broadest patent protection it is entitled to under the law. *Kingsdown Med. Consultants, Ltd. v. Hollister, Inc.*, 863 F.2d 867, 874 (Fed. Cir. 1988) (not inequitable to file an application to exclude a competitor's product, or to present claims intended to cover competitor's product learned of during prosecution).

Novozymes invented the 179,180 BSG alpha-amylase variants before February 1996, when it filed the first U.S. application in the '031 family, and disclosed these variants for improved thermostability and low calcium applications. **NPF, ¶38-51**. Novozymes was pursuing claims to the BSG variants by 2001, before Genencor turned to those variants for competitive advantage. **TE-101 at A7045-46; NPF, ¶45-51, 412; A5039:12-5041:1, A5049:9-24); A1006.** Genencor was well aware of Novozymes' "plan" to patent these variants, every step of the way, and in April 2004 it launched the Spezyme Ethyl product anyway. **NPF, ¶412**.

Novozymes diligently pursued the '031 application, and devoted R&D resources to an experiment which had been designed before it knew of Spezyme Ethyl. **TE-110 at A8169-71**. The experiment was intended to determine whether a comparison of the claimed 179,180 BSG variants to the closest prior art variants (Suzuki's 176,177 BAN) would show unexpected results. **NPF, ¶186**. The Borchert Declaration followed (**TE-508**), and the Examiner found that the comparison was appropriate, the results were unexpected, and she allowed the claims. **NPF, ¶64-66.** Novozymes reported this (publicly available) news to Genencor, so it could reconsider its Spezyme Ethyl "plan," but Novozymes was ignored. **A5014:4-14**. Accordingly, Novozymes brought suit to protect its intellectual property. **NPF, ¶119**. That Genencor chose an aggressive and risky competitive strategy cannot make an outlaw of Novozymes or its conscientious employees. That Novozymes naturally continued to seek patent protection in the face of Genencor's antagonism is not an indictment. That a patent issued in the midst of competition is not a reason to infer treachery; if anything it is a reason to respect and uphold the integrity of the patent system, which is concerned precisely with balancing innovation and commerce. *Kingsdown*, 863 F.2d at 874.

Genencor relies with bated breath on three cases, hoping that what happened there might rub off here. **GPTB, at 38-39**. In *eSpeed, Inc. v. Brokertec USA, L.L.C.*, 417 F.Supp.2d 580 (D. Del. 2006), the patentee withheld highly material prior art and made material misrepresentations when it was later disclosed. In *PerSeptive Biosystems, Inc. v. Pharmacia Biotech, Inc.*, 225 F.3d 1315 (Fed. Cir. 2000), the named inventors misrepresented the work of unnamed co-inventors on numerous occasions. In *Kao Corp.*, 441 F.3d 963 (Fed. Cir. 2006), the patentee disclosed only its most positive experiments, gave information about other experiments later, and had no deceptive intent and no inequitable conduct. There is no misconduct here either. Novozymes properly conducted and disclosed its only experiment. *Amgen Inc. v. Hoechst Marion Roussel*, 314 F.3d 1313, 1357-58 (Fed. Cir. 2003) (entire experiment not disclosed; no inequitable conduct). Machius was equitably not disclosed because it was not seen as material. *Tap Pharm. Prods., Inc. v. Owl Pharms., L.L.C.*, 419 F.3d 1346, 1352 (Fed. Cir. 2005). There was no intent to deceive and no pattern of misrepresentation, omission and half-truth. There was nothing to "cure," nor any fake cure. Genencor easily alleges egregious offenses to save itself, but the accusations are false.

1. There Was No Inequitable Conduct Surrounding Machius '95

From its one-sided view of the competitive landscape, Genencor alleges a dark misdeed. It says that that the Machius '95 reference is highly material, and was deliberately withheld from the PTO by Novozymes in order to dishonestly solicit the '031 patent. **GPTB, at 29-33**. However, the record actually shows that Machius was less relevant or cumulative of the closest prior art, because no alpha-amylase variants were made or tested, and no helpful theories were offered. **TE-173, A8384-85** (many unsatisfactory theories; no structures for variants). Machius was not material and did not have to be cited. 37 C.F.R. §1.56; *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1574-75 (Fed. Cir. 1997); *Pro-Mold and Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1576-77 (Fed. Cir. 1996).[3]

[3] Genencor argues that Machius makes explicit what the artisan would have known from Suzuki and Bisgärd-Frantzen. **GPTB, at 24 n.9**. This does not make Machius more pertinent; it (continued...)

Further, there was no intent to deceive the PTO, because Machius was not thought to be relevant, and there was not even a doubt about citing it. **NPF, ¶393-401**. There can be no inequitable conduct when there is no manifest intent to deceive. **NPF, ¶389-92**. *FMC Corp.*, 835 F.2d 1411 at 1415.

At most, Genencor claims that Machius adds a "loop" theory about why the Suzuki double-deletion worked for BAN and so might explain *post hoc* why BSG is also improved. Genencor cites Dr. Machius himself as characterizing this as a "no-brainer." **GPTB, at 29**. But Dr. Machius actually said he would "consider making the deletion a no-brainer." **A6562:21-22**. That motivation already came from Suzuki, not from Machius '95. The PTO Examiner found that this suggestion was already in the prior art from Suzuki and Bisgärd-Frantzen: the artisan would try a similar deletion in BSG, to get a similar effect on thermostability. **TE-101 at A7628**. Dr. Machius was in accord: "after Suzuki published his study, there was motivation to make the deletion in BSG." **A6562:3-5**; **A5040:1-5041:7**. There was no reason, and no legal need, to tell the Examiner what she already had found, or to repeat in Machius what the cited prior art already had been cited for. This is the essence of a "cumulative" reference. **NPF, ¶386-88;** *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 1582 (Fed. Cir. 1991).

Dr. Machius did say that with his paper and others, "a structural biologist, biochemist would have definitely expected a stabilizing effect upon the deletion." **A6563:1-18**. This is no more than what the Examiner already expected from the other references. **TE-101, A7627-28**. Dr. Machius unhesitatingly agreed with the other experts that the magnitude of any increase in BSG thermostability could not be predicted from his work. **A5721:21-5722:4; A6533:16-6535:19**. At most, some stabilization would not be surprising, but he could not say if it would really happen, or

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(…continued)
make it cumulative. Furthermore, Bisgärd-Frantzen aligns all three wild-type alpha-amylases and states that it is "possible to use the high degree of amino acid sequence homology observed between alpha-amylases" to prepare variants having improved properties, using "homologous position of the other homologous alpha-amylase." **TE-177, A8414:19-26**; **A8413-16** (alignments). There is nothing "explicit" or helpful in Machius that is not already found in the cited references.

if it would turn out to be more, less or similar to Suzuki. It was accepted in 1995 that a "loop," the whole basis of Genencor's argument, could (not would) stabilize or destabilize a protein. **A5720:20-5722:5.** Dr. Machius certainly gave no opinion that dramatically increased thermostability could be expected at both high temperature and low calcium. Neither he nor anyone else could have predicted an exceptional BSG variant of real-world significance, particularly well-adapted for extreme industrial use. **NPF, ¶352-55.** As Dr. Arnold explained, Machius would "definitely not" suggest the effect of the Suzuki deletion in BSG. **A6530:13-18**. Machius adds nothing material (**A6530:3-12**):

> I think that there is no additional information in the Machius reference. In fact, there is more confusion. It's just that given the Suzuki reference, one would have the impetus to make it but you don't know what is going to happen. You have to go and make the enzyme, you have to make the deletions, and you have to measure the effect.

Contrary to Genencor (**GPTB, at 30-31**), Dr. Borchert did not admit there was material information in Machius '95, not found in Suzuki. He was asked about what Suzuki does not teach, not what Machius does teach. **A5588:22-5589:7**. He did not find a 3D structure in Suzuki, but the artisan would still expect BLA, BAN and BSG to have similar 3D structures from the known homologies. **A5589:15-25**. What Dr. Borchert actually thought about Machius is found in his 2004 interference declaration, contemporaneous with the '031 prosecution. **TE-524, A8915-16 at ¶38-43**. Numerous problems with Machius made it unhelpful even in a case where crystal structures were specifically concerned. ***Id.,* A8906-08 at ¶6-7, 15-16, 38-43**. The '031 patent concerns specific amino acid deletions, not crystal structures, making Machius quite unhelpful here.

Genencor argues that given Dr. Borchert's "extensive familiarity with and multiple citations to the Machius '95 reference … [he] must have known of the materiality of Machius '95 ..." **GPTB, at 31**. But the contrary conclusion is apparent: Dr. Borchert was familiar with Machius and considered it carefully with Mr. Garbell in the concurrent interference. They never thought it was relevant. **NPF, ¶393-401**. Genencor's negative spin is not proof of inequitable conduct. *Dayco Prods., Inc. v. Total Containment, Inc.*, 329 F.3d 1358, 1367 (Fed. Cir. 2003) (no inference of

deceit, akin to a fraud, "simply from the decision to withhold a reference where the reasons given for the withholding are plausible."). Genencor also confuses knowledge of the *reference* with a presumption and knowledge of *materiality*; from which it then presumes, *ipso facto*, a manifest deceptive intent. This cruelly fashioned chain begins and ends with the sole fact that the reference was known and not submitted. Such misdirection and piling-on cannot lead to a clear and convincing finding of inequitable conduct. *Hebert,* 99 F.3d at 1116.

Genencor also argues (**GPTB, at 31**) that Mr. Garbell admitted the '031 patent might not have issued in view of Machius '95. What he really said was (**A5676:9-14**) (emphasis added):

> Q. If you disclosed Machius and the problems with the 132 declaration to Examiner Prouty, *and she put you under rejection based on Machius 1995*, you might still not have a patent; isn't that correct?
> A. That certainly is a possibility. I don't know one way or another.

Mr. Garbell agreed with a truism based on Genencor's assumption not in evidence: *if* the Examiner rejected the claims over Machius, it's *possible* the patent might not yet have issued; but no one really can know. He did not say or believe that the Examiner would have rejected the claims or that a patent would not issue. He testified to the contrary. For example (**A5660**):

> Q: Had she done that [cited Machius] your experimental work against Suzuki would have been useless?
> A: I disagree with that.

The experiment was proper regardless of Machius, and certainly not useless, because there was "an obligation to compare to the closest prior art, and that's the Suzuki reference." *Id*; **NPF, ¶252-53, 255, 393-401**. The claims were evaluated based on closer (more material) prior art (Suzuki and Bisgärd-Frantzen). That art was overcome by presenting Dr. Borchert's experiment. **NPF, ¶64-66**. Machius did not make the experiment predictable. The same results, good for Suzuki and Bisgärd-Frantzen, are also good for Machius. **NPF, ¶216-32, 249-56, 358-66, 393-401.**

Genencor trumpets that Mr. Garbell "made the connection between the disclosure in Machius '95 of the Suzuki reference and the '031 patent application," meaning he was "aware" that Machius was "relevant." **GPTB, at 31**. Yet, what Mr. Garbell actually said was that Machius "summarized the prior art to include the Suzuki reference." **A5671:23-5672:17**. Since Suzuki was

already disclosed, there was no need for Machius' summary. Furthermore, while "Machius has teachings other than what is in Suzuki, [Mr. Garbell] didn't consider any of those teachings material to the '031 patent prosecution." ***Id.***

In the end, Genencor extrapolates deceptive intent from the fact that Machius was not cited. Consideration of all of the circumstances belies that conclusion. There was no intent to deceive in not citing a references seen as immaterial, and which actually is immaterial. The circumstances, and what they portend, do not rise to inequitable conduct. *See also,* **Exhibit A**, attached.

Contrary to Genencor, **GPTB, at 25,** replacing one reference for others on the same grounds is cumulative. *Scripps*, 927 F.2d at 1582; **NPF, ¶56-66**. Notably, Genencor never shows how Machius could or should defeat Dr. Borchert's empirical findings or their import. **GPTB, at 29-33; GPF, ¶60-99; GCL, ¶89-95.**[4] Genencor argues that the Borchert results were defective on their own and should not have overcome Suzuki in the first place. **GPTB, at 33-38**. In fact, Dr. Borchert's results would not be any less unexpected compared to Machius than compared to Suzuki. *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d at 970.

The totality of circumstances also includes an explanation, and evidence of good faith. **NPTB, at 36-37**; *Kingsdown,* 863 F.2d at 876. The interference declaration is contemporaneous evidence of good faith by Novozymes employees Garbell and Borchert. What they thought about Machius at that time confirms their testimony at trial. They believed that Machius is defective and immaterial. **TE-524, A8915-16, ¶38-43**. In compliance with the duty of candor, they cited the material prior art early on: Suzuki is in the '031 application itself. Bisgärd-Frantzen was in an early Information Disclosure Statement. **TE-100, at A7242**. Novozymes devoted time and resources to comparison tests, to see if it could distinguish what it and the Examiner thought was

[4] For example, Genencor says that Novozymes did not use proper experimental conditions from "the closest prior art," i.e. Suzuki's conditions. **GPTB, at 34-35**. But Genencor does not say that Machius provides conditions or guidance to supplement Suzuki. In fact, Machius made no variants and no empirical comparisons among alpha-amylases, as Suzuki did. **TE-173 at A8375-90**.

the closest prior art, and is the closest prior art. There was no "plan" by Novozymes to withhold Machius, with an intent to deceive, knowing or believing that it was material.

2. The Borchert Declaration

Genencor spent much of the trial minutely criticizing almost every aspect of the Borchert experiments and resulting Declaration. **A6549:23-6550:15**. Yet, at the end of the day Genencor cannot escape that the claimed invention does provide superior and unexpected thermostability, sought after by customers. Genencor adopted as its own the same variant successfully tested by Dr. Borchert, and which has enjoyed significant commercial success. **NPF, ¶120-27, 236-37** Simply stated: the conclusions in the Borchert Declaration are true. The experiment supports those conclusions, and it was properly done and reported. **NPF, ¶181-215, 257-65, 349-52, 402-08**.

Genencor first complains about the timing of the Declaration, insinuating that Novozymes had a "plan," and somehow wrongly presented the Declaration to the Examiner when a rejection was not pending. **GPTB, at 34**. Genencor fails to say what might be improper about this "plan," because indeed there was nothing wrong with it. When the Declaration was submitted, Novozymes sought to reinstate broader claims, which issued as the '031 patent claims. In fulfillment of its duty of candor, Novozymes reminded the Examiner that broad 179,180 deletion claims "were previously rejected … as obvious over Suzuki et al … in view of Bisgärd-Frantzen." **TE-101, A7736**. Novozymes stated that "even though there is no outstanding issue on obviousness, Applicants wish to establish on the record that new claims 48-52 [the issued '031 claims] are patentable over the prior art." ***Id***. This is evidence of good faith and candor, not a conspiracy to mislead. *Kingsdown,* 863 F.2d at 876.

Genencor next complains that Dr. Borchert used conditions that differed from those in Suzuki for measuring thermostability, and did not point out these differences to the Examiner. Genencor misunderstands the law on the first point, and is plain wrong on the second point.

Unexpected advantageous properties may rebut seeming obviousness based on structural similarities. *In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987). The proper comparison is with the

closest prior art, and deviations are to be noted for the PTO. MPEP 716.02(e); *In re Finley*, 174 F.2d 130 (CCPA 1949); *In re Merchant*, 575 F.2d 865, 869 (CCPA 1978). Crucially, the "closest prior art" depends on what is claimed. *Id.* at 868. The '031 claims are for 179,180 BSG variants; no conditions of temperature, calcium etc. are claimed. It is not necessary to test all variations in the references, nor is there any requirement to recite unexpected results in the claims. *In re Chupp,* 816 F.2d at 646. Suzuki is the closest prior art because it discloses the BAN enzyme with a double-deletion at positions 176, 177, not because it used test conditions of academic interest to Suzuki, but inapplicable to industry. **TE-101 at A7627-28**.

Good testing certainly includes conditions relevant to the invention and its purpose, such as industrial conditions. *In re Merchant*, 575 F.2d at 869-70 (conditions for commercial operation showed unexpected results); *Application of Snoddy*, 420 F.2d 381, 383-384 (C.C.P.A 1970) (detergent composition compared to prior art compositions under same end-use conditions). It is certainly reasonable to consider whether the prior art solved the problem of the invention, or whether the invention unexpectedly did so despite the closest prior art. *In re Dillon,* 892 F.2d 1554, 1562-63 (Fed. Cir. 1989) (problem and solution compared to prior art). Suzuki did not address thermostability at high temperature and low calcium, as the '031 patent did. It is not relevant, and certainly less relevant, how the invention might perform under other conditions of scholarly interest in the prior art, and different from its working environment. **NPF, ¶186-87, 193-99, 350, 404-05**. In other words, the closest prior art is best compared to the invention, under conditions meaningful to the invention; not the other way around. By analogy to reduction to practice of the invention, there should be a relationship between the test conditions and the intended functional setting, *Paivinen v. Sands*, 339 F.2d 217, 226-227 (C.C.P.A. 1964); *Knowles v. Tibbets*, 347 F.2d 591, 594 (C.C.P.A. 1965); Voisinet v. Coglianese, 455 F.2d 1064, 1068 (C.C.P.A. 1972). The core of Genencor's argument is that a fish should be tested out of water. This cannot be correct.

Along the same lines, there were no deviations from the prior art that Dr. Borchert failed to properly disclose or explain. He clearly disclosed at ¶4 of his Declaration that he employed a BAN

variant having the deletion R176-G177 (BANdel) for his comparison. **TE-508, A8858, ¶4**. No one says this was not the right Suzuki variant for the experiment.

Dr. Borchert explained that: "80 degree Celsius was chosen as the highest temperature where both BAN and BSG wild-type and derived variants could be reliably compared." ***Id*, ¶5**. That Suzuki did tests for BAN vs. BLA at a 90° C is not binding on testing for unexpectedly superior thermostability of BAN vs. BSG. (Suzuki did not have the BSG enzymes of the invention.) In any case, 80° is close to Suzuki's 90° and is appropriate for comparing enzymes intended for harsh industrial applications. **NPF, ¶193-95**. Genencor has not shown that a 90° test would matter. Further, its own patent application discloses and claims that 60-80° C is suitable for starch liquefaction, using the same alpha-amylase variants. **TE-202, A8532.45** (claim 16).

Dr. Borchert also disclosed that 0.1 mM calcium was used in his experiment. **TE-508, A8859, ¶5**. This was not a "deviation" from Suzuki's 10 mM calcium that had to be further explained, because comparing the thing itself, the variant, is what matters. Also, Suzuki used so much calcium that no one interested in real-world consequences would follow his example. **NPF, ¶196-99**. A 0.1 mM calcium level was appropriate for fuel ethanol production (***id.*, ¶196**), and was an accepted calcium level in the field (***id.*, ¶196-99**). The '031 patent discloses 0.1 mM calcium, and a stated object of the invention is to provide a less calcium dependent enzyme. **NPF, ¶196.** This could not have been tested at Suzuki's conditions, and is a further unexpected result that Genencor overlooks. Bisgärd-Frantzen, cited with Suzuki, discloses 0.1 mM calcium, so an appropriate calcium level from the cited art <u>was</u> used. **TE-177, A8447 at 5-9**. It is strange to insist, and quite wrong, that using less calcium than Suzuki and saying so, was inequitable conduct.

Genencor makes the startling claim that since Novozymes contends that no one could predict the effect of the BSG double-deletion, then any improvement could not be surprising. **GPTB, at 35**.[5] This circular argument shows how far Genencor will go to sow confusion. An

[5] Genencor relies on Dr. Borchert for this idea, but mischaracterizes his testimony. He said that he expected that BSG could be stabilized, but he could <u>not</u> predict how much. **A5641:10-19**.

invention is not obvious when its advantages cannot be foretold. *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). This is what the Declaration evaluated and disclosed. A lack of predictability cannot be transmuted into an expectation of dramatic success. To say that no one should be surprised by the unexpected may be philosophical, but is legally irrelevant, and cannot lead to inequitable conduct.

In conducting the experiment in the Declaration, Dr. Borchert and his technicians accurately and fairly reported the data collected and the results they obtained. **A5640:19-5641:1; A6092:11-14**. As was clear from the expert testimony of both Drs. Klibanov and Arnold, it is routine in science to discard questionable measurements based on sound scientific principles. There is no ethical or legal obligation to include such measurements with the reported data. **NPF, ¶207-13, 407**.

As Dr. Klibanov explained, when a scientist drops his sandwich into a test tube, the measurement obtained would be properly excluded. **A6020:9-24**. The fact that it was excluded would not be expected to be reported. ***Id.*; NPF, ¶207-13, 407.** These things happen all the time: (a) substrate was visually detected in one of the two assays for each 20 and 40 minute BSG sample, requiring those measurements to be discarded; however the parallel measurements were fine and were used (**A6080:3-14; NPF, ¶209**); (b) Evaporation was found in the heated 2881 minute BSGdel sample; so everyone agrees it could not be used (**NPF, ¶210**); and (c) activity greater than 100% was found in a BSGdel sample heated for several days (2940 minutes), and the parallel reading was so different that neither reading could be used (**NPF, ¶211-12**).

Genencor, of course, would portray good judgment as part of a grand scheme to present faked evidence of unexpected results. It has been affirmatively shown that this was not the case at all. **NPTB, at 34-40**. In addition, the Court asked a significant question at trial, overlooked by Genencor: what happens when these measurements are included? **A6016:7-25**. Dr. Arnold explained that, apart from the 2881 minute data that she and Dr. Klibanov agreed should have been left out (**A6549:7-20**; **A6020:14-24**), and including all combinations of the 2940 minute readings, the "whole range of possibilities" takes the relative improvement for BSG del from 55 to 77 fold. The result is a 5 to 7 fold improvement compared to BAN, which corresponds well with the 5-6

fold improvement stated in the Declaration. **NPF, ¶212**. The alleged problem of ramp-up time would not have materially closed the gap or made a difference either. **A5645:22-25.** Notably, Dr. Borchert also did not rely on the higher degree of improvement that one reading of the data would support (77-fold), corroborating that his decisions were honest and scientifically sound.

Genencor and Dr. Klibanov did not do any experiments or calculations. When the Court asked Dr. Klibanov about counting the excluded measurements, he answered that the improvement falls to "way under a factor of two," which he represented was in his first expert report (not in evidence). **A6017:19-6018:11**. Yet, Dr. Klibanov conceded at trial that it was correct for Dr. Borchert to exclude the measurement at 2940 minutes that exceeded 100% (**A6019:5-10**); and it was correct to exclude measurements when you see something wrong (like those at 2881 minutes where evaporation was seen). **A6019:11-17; A6020:4-13**. *Worse, Dr. Klibanov conceded that his conclusions were not based on actual data: he made it up, for purposes of illustrating his opinion -- his unsubstantiated opinion.* Thus, (**A6014:1-23**) (emphasis added):

> Q. Doctor, I just wanted to be clear. . . . There is fictitious made-up data. This is not real data from this case; correct?
>
> * * *
>
> A. Yes. As I said, these are just representative arbitrary data to illustrate the point I just made.

See also, **A6018:2-11, A6552:25-6553:22**.[6] If anything, Genencor and Dr. Klibanov fabricated data and overstated results to this Court; Novozymes did not do so in the PTO.

It is telling that while Genencor did no experiments here, it does do such experiments all the time and discloses its protocols in patent applications; including one for the 179,180 BSG deletion. **NPF, ¶206; TE-202, at A8532.26**. Genencor does not worry about things like preheated buffer or ramp up time; but accuses Novozymes of perfidy here. ***Id***. If Dr. Borchert's data had been

[6] Genencor relies on Dr. Klibanov to complain about pre-heated buffer and ramp-up time; speculating that this would bring BAN closer to BSG. **GPTB, at 35; A6014-2-23**. However, he did not do any experiments, nor did he consider the ramp-up work done by Novozymes. **A6543:6-6544:21**. Given the actual experiments by Dr. Tams and Ms. Egede for Novozymes, Dr. Arnold found that in practice, "I think the ramp-up time had essentially no effect." **A6545:25**.

fabricated, or just off-base, the Court would undoubtedly have seen, with great fanfare, the results of Genencor's own experiments showing less of an improvement than Dr. Borchert found. No such work has surfaced, and the reason is simple: Dr. Borchert's experiment accurately reflects reality. **NPF, ¶123, 402-08**. If the BSG difference was only marginal, Genencor would not be touting the industrial benefits of Spezyme Ethyl, and would not have filed its own patent application covering the same technology. **TE-202, at A8532.1-8532.45; TE-194, A8521**. As Dr. Arnold noted, Dr. Borchert's experiments demonstrate that the double-deletion in BSG provides an enzyme that keeps working for *days* at 80° C. Without the deletion, the BSG enzyme loses most of its activity after a few *hours*. **A6534:24 - A6535:19**. The prior art variant at best lasted only for *minutes*. **NPF, ¶192; TE-508; A8860 at ¶7**. This is an unexpected result, and is important in an industrial setting.

The Borchert work was properly designed, carried out, and reported to the PTO. There was no material misrepresentation and intent to deceive. There can be no finding of inequitable conduct.

B. THE '031 CLAIMS ARE VALID

1. Claims 1, 3 and 5 Are Non-Obvious

A claim is obvious only when "the prior art would have suggested to one of ordinary skill in the art that [the claimed invention] should be carried out and would have a reasonable likelihood of success.... Both the suggestion and the expectation of success must be found in the prior art, not in the applicant's disclosure." *In re Dow Chemical*, 837 F.2d 469, 473 (Fed. Cir. 1988). The person of ordinary skill could not have foreseen the significant industrial improvement in BSG, which made it a viable product. **NPF, ¶229-32, 363-66**. Even assuming some increase in thermostability was reasonable to expect, the unpredictable magnitude and importance of the improvement makes for a non-obvious and patentable improvement. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991) (warning against hindsight). Genencor has not meet this standard, has not rebutted the evidence of unexpected results, and has not shown a clear and convincing case of invalidity.

(a) The Combination of Suzuki and Bisgärd-Frantzen Does Not Make the '031 Claims Obvious

Suzuki (**TE-115, A8233-38**) describes mutants of an alpha-amylase enzyme from another *Bacillus* species, *B. amyloliquefaciens* or "BAN" (a/k/a "BAA"). Some of these mutants were modified to be more like the alpha-amylase from another *Bacillus* species, *B. licheniformis* ("BLA"). One BAN mutant had a deletion of two amino acids, Arginine 176 (R176) and Glycine 177 (G177), and had improved thermostability, compared to the wild-type BAN alpha-amylase it was made from. Bisgärd-Frantzen (**TE-177, A8403-8507**) describes alpha-amylases from BAN and BLA, as well as *B. stearothermophilus* ("BSG"), and teaches that these enzymes have highly homologous amino acid sequences. Bisgärd-Frantzen aligned these enzymes and suggested homologous alterations. Suzuki's 176,177 deletion in BAN aligns with 179,180 in BSG. ***Id.***

The Examiner's § 103 obviousness rejection was straightforward. She thought it would have been obvious to introduce Suzuki's mutations into the corresponding positions of BSG alpha-amylase, in order to produce a homologous alpha-amylase, which would be reasonably expected to have similar properties, in view of the homologies from Bisgärd-Frantzen. **TE-101, at A7628**. However, this did not establish *prima facie* obviousness, and Novozymes has never said that it did.[7]

Indeed, Dr. Arnold testified regarding the 179,180 deletion in BSG that "one would have the impetus to make it (motivation); but "you don't know what is going to happen," you have to try it and "measure the effect" (no expectation of success). **A6530:9-12**. Indeed a similar deletion in the Igarashi paper actually made things worse. **A6529:7-15**. Dr. Zeikus testified for Genencor that there was, *at best*, only a 50/50 chance that the R179, G180 BSG deletion would increase stability. **A6107:8-12**. So, the deletion was <u>not</u> reasonably expected to work. It was more likely than not to produce no improvement at all, let alone an improvement similar to Suzuki. Dr. Machius testified likewise that in 1995, a person of ordinary skill could not have predicted "if there was any

[7] Genencor invites the Court to reinstate the PTO's rejection. **GPTB, at 21**. However, we are not in the PTO. The propriety of the Examiner's initial rejection will not suffice to invalidate the '031 claims. The burden is on Genencor to make its case at trial by clear and convincing evidence, subject to the presumed validity of the patent. 35 U.S.C. §282. Genencor has not done so.

stabilization at all." **A5721:21-25**; **A5722:1-4**. Success is not reasonably expected when its kind or degree was unpredictable. *In re Soni*, 54 F.3d 746, 750-51 (Fed. Cir. 1995). There was no reasonable expectation of success, and no *prima facie* obviousness under §103.

(b) The Borchert Declaration Demonstrates Unexpected Results

Genencor has not disturbed the strong presumption that Novozymes and the PTO did their jobs properly, and claims 1, 3 and 5 of the '031 patent are valid. 35 U.S.C. §282. Genencor failed to establish the foundation of obviousness: that the prior art suggested the invention, and in making or carrying it out, "those of ordinary skill would have a reasonable expectation of success." *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991); *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006); **NPTB, at 27**. The suggestion and the expectation of success must be found in the prior art. *In re Dow Chemical,* 837 F.2d 469, 473 (Fed. Cir. 1988). An affirmative showing that the results are unexpected will preclude obviousness. *In re Soni*, 54 F.3d at 750-51.

The 179,180 deletion in BSG was unpredictable. Genencor and its experts did not prove otherwise by clear and convincing evidence. As Dr. Machius explained, a person of ordinary skill in the art in 1995 "would not have been able to predict the magnitude of stabilization in BSG, or to compare or to know if there was any stabilization at all." **A5721:21–5722:4**. Genencor has failed to discredit the Borchert Declaration and its demonstration of unexpected results. *See also* §III.A.2, above. Novozymes compared its 179,180 BSG variant to the closest prior art. **NPF, ¶350**; § III.A.2, *supra.* The comparison was relevant to the industrial use of these enzymes; including low calcium (a goal of the invention), and an industrial temperature of 80 °C suitable for all the samples.[8] Suzuki's conditions were not relevant. For example, Dr. Zeikus confirmed that 10 mM calcium was "extremely high" (**A6114:18-24**), and high calcium is a problem for fuel ethanol production. **NPF, ¶44**. There is nothing here from which to invalidate the patent.

[8] **TE-100 at 1:21-24, 2:61-66, 4:7-12**; **A6092:15-25**; **A6114:18-20**; **A6535:20-6536:11** (calcium); **A6536:24-25**; **A6536:12-6537:25**; **A6067:21-6077:4**; **A6094:8-A6096:6** (temperature).

The Declaration positively shows non-obviousness by demonstrating that the 179,180 BSG deletion increases stability 63-fold; or 5-6-fold (63/11=5.7) more than Suzuki's 11-fold BAN mutant. **NPF, ¶349**. Genencor argues, based on Dr. Klibanov's unsubstantiated testimony, that such results are not surprising. **GPTB, at 21-22**. Klibanov gave no explanation or support for his assumptions. **A5818::4-5**. He ignored that the 63-fold improvement in BSG has a "very apparent" practical effect (**A6534:24**) especially in fuel ethanol production where alpha-amylases must work for hours at high temperatures and low calcium. **NPF, ¶353**. He relied on "arbitrary data," (**A6014:1-23**), and his subjective view of the Declaration data (*compare* **GPF, ¶107-134** *with* **NPF, ¶181-215**). He did not consider other experiments (**NPF, ¶203-05**), and did not do or supervise any of his own. **NPF, ¶185, 203**. Even Genencor admits that the properties of the claimed variant, like its Spezyme Ethyl, were a key advance over lesser enzymes that were unsuitable for demanding, real-world conditions and could not compete. **A5034:4-10; A5036:23-5037:14**.[9]

The so-called "numerous deficiencies" in Dr. Borchert's experiment are not deficiencies at all, as demonstrated at trial and in **§II.A.2**, above. Appropriate conditions were used (**NPF, ¶193-99**), and the samples and readings were handled appropriately (**NPF, ¶207-13**). For example, Dr. Borchert used PCR thermocycler equipment to rapidly heat samples and address ramp-up time, which made it reasonable to forego preheating the buffer in his experiment. Genencor does the same in its own protocol. **A6538:19-20; A6540:15-25; NPF, ¶200-06**. Dr. Klibanov may have said that preheating was standard more than 30 years ago. But that was before thermocyclers were available. **A5756:9-12**. By 1995 this was an outdated practice. **A6541:21-25**. And ramp-up time did not change the overall results and conclusions anyway. **NPF, ¶204-05**.

Genencor's Dr. Crabb also characterized routine thermostability testing (**A5053:6-12**):

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[9] The BSG variant is an improvement in kind, not just in predictable degree. BSG wild-type has a half-life of ~1.5 hours at 80 °C, the BSG variant is still potent after 4,200 minutes (~3 days). The closest prior art, BAN wild-type and its deletion variant, have half-lives of less the 1 and 10 minutes, respectively, under the same conditions. ***Id.*** No one could have predicted such a great leap forward. **A5721:21-5722:4**; **TE-508, A8860 ¶7; A6534:24-6535:4**.

> Typically, you would design a buffer at zero calcium, add calcium at defined increments, add an enzyme at defined increments, place those in a predetermined temperature bath, take samples at a time frame, usually from zero to perhaps 10 minutes, and measure residual activity ….

He does not note a pre-heated buffer, and everything is put in a temperature bath after enzyme has been added. This testimony; does not establish that pre-heating the buffer is routine. **GPF, ¶110**.

Again, Genencor does not offer any other data or results to support a different conclusion. **A6549:21-6550:15**. Its expert did not consider any real empirical data (only "arbitrary data") (**A6014:1-23**). Dr. Arnold did consider other experiments and she found, (**A6550:3-15**):

> [W]e've looked at that [Borchert Declaration] from both sides with every possible criticism. And my conclusion after seeing all of this is that it's a fair representation of what actually is going on with those enzymes. I would also like to mention that I have seen no counter data. . . . These are experiments that people, especially with the resources that we're talking about, can do.

Contrary to Genencor, the '031 claims are non-obvious and patentable over Suzuki, with or without Bisgärd-Frantzen, because there is no conclusive showing of *prima facie* obviousness. Moreover, there are tangible unexpected results of a high degree and with important practical significance.

(c) Machius '95 Does Not Render the Claims Obvious

Machius '95 is cumulative and does not add to the teachings of Suzuki and Bisgärd-Frantzen. Genencor has not shown otherwise. Genencor in particular fails to show that the marked superiority of the claimed 179,180 BSG variants, at high temperature and low calcium, was predictable from Machius. The actual testimony of record is to the contrary. Everyone, including Dr. Machius himself, in the end agreed that the fact of the improvement and its magnitude could not have been expected. **A5720:20-5722:5**

Obviousness is determined by considering the differences between the prior art and the claimed invention. Those differences most prominently include practical results, and whether they were unpredictable. *In re Soni*, 54 F.3d 746, 750-51 (Fed. Cir. 1995). Objective criteria of non-obviousness must also be considered, such as long-felt need, failure by others, and commercial success. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

Contrary to Genencor, Machius does not address the "identical problem as the '031 patent," **GPTB, at 23**. Machius is concerned with solving the crystal structure for a *B. licheniformis* alpha-amylase (**TE-173, A8375-8390; NPF, ¶217-19**), not claimed in the '031 patent. **TE-100, at A7040**. Machius failed even in solving that structure - the alpha-amylase he crystallized was cut in two, was calcium depleted and was missing information about key amino acids. **NPF, ¶220-28**. Machius made no alpha-amylase variants; he was not trying to make better industrial enzymes or solve any problems in doing so; and he did not provide any new solutions.

Genencor is wrong that Machius provided "increased motivation" by proposing a speculative loop theory for "why" Suzuki's deletion in BAN might have increased its thermostability relative to BLA. Once Suzuki had succeeded, the idea was fully in hand to try that deletion in another enzyme. The motivation was complete and a later reason "why" it might have worked is irrelevant. **A6526:5-6; A6527:19-23; A6529:1-6530:2**. Plus, the Machius "why" was really a "maybe," and did not make success any more predictable. The proposed "loop" idea was one of many, all unsatisfactory and confusing. **NPF, ¶229-32**. The theory still could not predict success or failure, much less the quantum leap Dr. Borchert actually observed. **NPF, ¶362-66**. Dr. Machius admitted that with Machius '95 in hand, neither he nor an ordinary skilled artisan could have predicted the magnitude of the 179,180 BSG deletion, or if it would have had a good effect at all. **A65623-25; A5720:20-5722:4** ("Loops, in general, can have any effect"), **A5720-5722**.

Moreover, Dr. Borchert's results overcome Machius. The 63-fold increase in BSG has a "very apparent" practical effect in fuel ethanol production (**A6534:24**); it keeps working for days, not hours or minutes. **A6534:24-A6535:19**. Genencor's reliance on *Richards-Vicks, Inc. v. Upjohn Co*, 122 F.3d 1476, 1484 (Fed. Cir. 1997) is of no help. There, the "result" was a predictable affect of using two known drugs together in one tablet (ibuprofine and pseudophedrine), when they were already being co-administration by doctors. Here, no one had made or tested the BSG variants before Novozymes and no one could predict their performance or that it would be so good.

Machius does not establish that any claim of the '031 patent is obvious and invalid.